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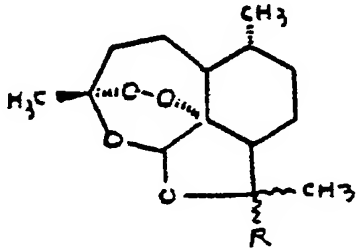
(54) **9-Substituted compounds of 3 alpha, 11 alpha-Epoxy-3,4,5, 5a alpha,6,7,8,8a,9,11,11a-undecahydro-3 beta, 6 alpha, 9-trimethylfurano[3,4-j][1,2]-benzodioxepin, processes for their preparation and their use as antiprotozoal and antiviral agents.**

(57) Compounds of formula I



in which the substituted R has the given meaning, have an antimalarial and an antiviral activity.

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may also contain chiral centers contributing to the optical properties of the compounds of the present invention and providing a means for the resolution thereof by conventional methods, for example, by the use of optically active acids. A wavy line (~) indicates that substituents can either be in the α-orientation or β-orientation. The present invention comprehends all optical isomers and racemic forms of the compounds of the present invention where such compounds have chiral centers in addition to those of the furano(3,4-j)-(1,2) benzodioxepin nucleus.

The term alkyl stands for C_1-C_8 straight or branched chain carbon compounds such as methyl, ethyl, propyl, butyl, isopropyl, t-butyl. The term alkenyl stands for straight or branched chain carbon compounds containing one or more double bonds. Suitable examples are acryl, stearyl, cinnamyl.

The term alkynyl stands for straight or branched chain carbon compounds containing one or more triple bonds and may in addition contain a double bond. Examples of alkynyl groups are 3-methyl-1-pentynyl, 1-butynyl, 3-methyl-1-butynyl, 2-butynyl-1-hydroxymethyl.

Substituents of substituted alkyl, alkenyl and alkynyl are halogen, hydroxy, carboxy, nitrile, acyl, aryl, heterocycle or a group NR_6R_7 , wherein R_6 and R_7 are as defined above.

The term aryl stands for a phenyl group which is optionally substituted by one or more substituents such as halogen, alkyl, nitro, amino, hydroxy, alkoxy, carboxy, alkylcarboxylate, trifluoromethyl, substituted amino, acetyl, alkenyloxy, alkynyloxy. The term heterocycle stands for a cyclic group containing one or more hetero atoms such as piperazino, morpholino, piperidino, pyrrolidino, phthalimido, optionally substituted at one or more places by alkyl, alkoxy, hydroxy, halogen or aryl groups.

Preferred compounds of the invention are listed in Table 1.

Further preferred compounds of the invention are those of formula I, wherein R stands for a group CHO or CH_20R_2, wherein R_2 has the same meaning as defined above.

Particularly preferred compounds of the invention are

3α,11α-Epoxy-3,4,5,5aα,6,7,8,8a,9,11,11a-undecahydro-9-formyl-3β,6α,9-trimethylfurano[3,4-j][1,2]-benzodioxepin,

3α,11a-Epoxy-3,4,5,5aα,6,7,8,8a,9,11,11a-undecahydro-9-(2-propynoxy)methyl-3β,6α,9-trimethylfurano[3,4-j]-[1,2]-benzodioxepin,

3α,11α-Epoxy-3,4,5,5aα,6,7,8,8a,9,11,11a-undecahydro-9-(2-propenoxy)methyl-3β,6α,9-trimethylfurano[3,4-j]-[1,2]-benzodioxepin,

3α,11α-Epoxy-3,4,5,5aα,6,7,8,8a,9,11,11a-undecahydro-9-(p-toluenesulfonyloxy)methyl-3β,6α,9-trimethylfurano-[3,4-j][1,2]benzodioxepin,

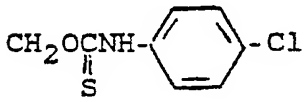
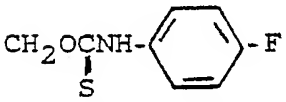
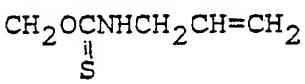
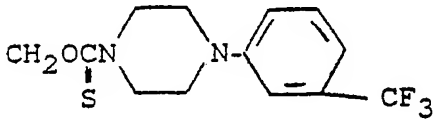
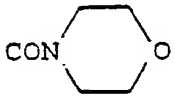
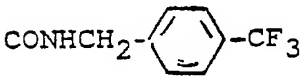
3α,11α-Epoxy-3,4,5,5aα,6,7,8,8a,9,11,11a-undecahydro-9-(4-chlorophenylaminothiocarbonyloxy)methyl-3β,6α,9-trimethylfurano[3,4-j][1,2]benzodioxepin,

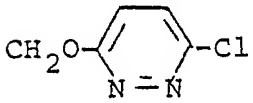
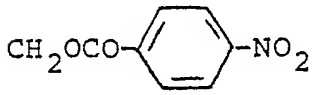
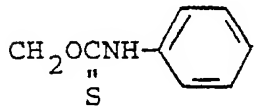
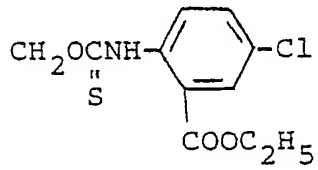
3α,11α-Epoxy-3,4,5,5aα,6,7,8,8a,9,11,11a-undecahydro-9-(4-fluorophenylaminothiocarbonyloxy)methyl-3β,6α,9-trimethylfurano[3,4-j][1,2]benzodioxepin,

3α,12α-Epoxy-3,4,5,5aα,6,7,8,8aα,9,10,12β,12a-dodecahydro-10α-[3α,11α-epoxy-3,4,5,5aα,6,7,8,8a,9,11,11a-undecahydro-3β, 6α,9-trimethylfurano[3,4-j][1,2]benzodioxepin-9-methylen]oxy-3β,6α,9β-trimethylpyrano-[4,3-j][1,2]benzodioxepin and

3α,12α-Epoxy-3,4,5,5aα,6,7,8,8aα,9,10,12β,12a-dodecahydro-10β-[3α,11α-epoxy-3,4,5,5aα,6,7,8,8a,9,10,11,11a-undecahydro-3β,6α,9-trimethylfurano[3,4-j][1,2]benzodioxepin-9-methylen]-oxy-3β,6α,9β-trimethylpyrano[4,3-j][1,2]benzodioxepin.

Table 1 (cont.)

R	M.P. °C	% Yield
	89-90	42
	79-80	37
	Oil	23
	69-71	22
	Oil	43
	93	43
	170-172	25
$COOCH_2CH_2Cl$	112	46
$COOCH_2CH=CH_2$	Oil	38
$CH=CH-COOC_2H_5$ (cis)	Oil	54
$CH=C(COOC_2H_5)_2$	Oil	22

R	M.P. °C	% Yield
	150-152	72
CH_2OCOH	84	55
CH_2OCOOH	98- 99	36
	158-159	64
	81- 82	44
	oil	27

The process for the preparation of compounds of the invention comprises the reaction sequence outlined in the scheme 1 wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9 have the same meaning as described above.

The process comprises treatment of compounds of the formula II [prepared as reported in J. Med. Chem. 1989, 32, 1249-1252] with a brominating agent, preferably with liquid bromine using halogenated hydrocarbon as solvent such as carbon tetrachloride and preferably stirred for a period of one hour, then quenching with water and isolating the product of formula III from the organic layer as described herein.

then worked up by concentration under vacuum and the residue obtained is purified by chromatography on adsorbent such as silica gel and using eluent such as chloroform to obtain compounds of the formula Ia.

Compound of the formula 1b is prepared from compound of formula Ia by treatment with reducing agents preferably such as sodium borohydride using alcohols such as ethanol, methanol, isopropanol as solvents, preferred being ethanol at temperatures ranging from 0 to 30°C preferably at 27-30°C for a period of 15 minutes to 60 minutes preferably for thirty minutes. After the completion of reaction mixture is treated with aqueous solution of ammonium chloride and then concentrated under vacuum to remove ethanol. Residue is extracted with organic solvents such as ethylacetate, chloroform, dichloromethane. Organic layer is then separated and washed with water, dried over drying agents such as sodium sulfate and then concentrated. The residue obtained is purified by chromatography preferably over silica gel using eluant such as mixture of ethylacetate and chloroform to obtain compound of the formula 1b.

Compound of the formula Ic is obtained from compound of the formula Ia by treatment with oxidising agents preferably such as aqueous silver nitrate solution in the presence of an aqueous alkaline solution such as sodium hydroxide or potassium hydroxide and an organic water miscible solvent such as ethanol, methanol preferably being ethanol at temperatures from 0°C to 45°C, preferred being 27-30°C for a period from one hour to six hours, preferably for two hours. The reaction mixture is then filtered, concentrated and the residue is extracted with organic solvents such as ethylacetate or halogenated hydrocarbons such as chloroform, methylenechloride. Extracts after washing with water are dried over drying agents such as sodium sulfate and then concentrated. Residue obtained is purified either by crystallisation or by chromatography to obtain compounds of the formula Ic.

Compounds of the formula Id, wherein R_2 has the same meaning as defined earlier except 3α,12α-Epoxy-3,4,5,5aα,6,7,8,8aα, 9,10,12β,12a-dodecahydro-3β,6α,9β-trimethylpyrano[4,3-j][1,2]-benzodioxepin-10-yl are prepared from compound of formula 1b by alkylation, preferably in the presence of a base such as sodium hydride in an anhydrous organic solvent such as benzene, toluene or dimethyl formamide, preferably dimethylformamide and halide of the formula R_2X', wherein R_2 has the same meaning as defined above and X' stands for halogen such as chloro or bromo at temperatures initially ranging from 0°C to 30°C, preferably at 0-5°C for a period from 5 minutes to 60 minutes preferably for 10-15 minutes and then at temperature 27°C for a period of one to six hours preferably for two hours. Reaction mixture after dilution with water is extracted with organic solvents such as petroleum ether, chloroform, ethylacetate and extracts after treatment with water and drying agents are concentrated and purified by column chromatography but in the case of compounds wherein R_2 has a basic group, reaction mixture is purified from organic solvent extract by acid base treatment to obtain compounds of the formula Id.

Compounds of the formula Id wherein R_2 stands for 3α,12α-Epoxy-3,4,5,5aα,6,7,8,8aα,9,10,12β,12a-dodecahydro-3β,6α,9β-trimethylpyrano[4,3-j][1,2]benzodioxepin-10-yl are also prepared from compound of the formula 1b by treatment with dihydroartemisinin, preferably in the presence of a catalyst such as borontrifluoride etherate at 0°C using organic solvent such as anhydrous methylene chloride for a period of fifteen minutes to one hour. The product is isolated from the reaction mixture by washing the reaction mixture with water, drying the organic layer, filtering and concentrating the filtrate under vacuum. Final purification is done by flash column chromatography using silica gel column to obtain α and β isomers.

Compounds of the formula Ie are prepared from compound 1b by treatment with a mixture of acid chlorides of the formula R_3COCl, wherein R_3 has the same meaning as defined above, preferably in the presence of an organic base such as N,N-dimethylaminopyridine, triethylamine or pyridine preferred being N,N-dimethylaminopyridine in organic solvent such as chloroform or dichloromethane at temperatures ranging from 0 to 35°C, preferably at 27-30°C for a period of one hour to six hours preferably for three hours. The reaction mixture is then diluted with water, extracted with organic solvent such as petroleum ether and petroleum ether extract is then washed with dilute hydrochloric acid followed by water and dried over anhydrous sodium sulphate and then concentrated. Residue is purified by chromatography to obtain compounds of the formula Ie.

Compounds of the formula If are prepared from compound of formula Ib by treatment with compound of formula R_4SO_2Cl preferably in pyridine wherein R_4 has the same meaning as defined earlier at temperatures ranging from 50 to 120°C, preferably at 90-100°C for a period of one to six hours, preferably for three hours. The reaction mixture after cooling to room temperature is diluted with water followed by extraction with organic solvents such as ethylacetate.

The ethylacetate extract is washed with dilute acetic acid, water, aqueous sodium bicarbonate and water in sequence and dried over anhydrous sodium sulfate and then concentrated after filtration to get residue which is purified by chromatography over silica gel to get compounds of formula If.

Compounds of the formula Ig are prepared from compound Ib by treatment with compounds of formula R_5NCX in an organic base such as triethylamine, diethylamine, benzylamine, N,N'-dimethylpyridine or

A. For Antimalarial Activitv

The evaluation of blood-schizontocidal activity "28-day test" described by Raether and Fink [W.H.O. Report on the Scientific Working Group on the Chemotherapy in Malaria, TDR/Chemal 3rd Review, 85.3, Geneva, 3-5 June 1985 and references contained therein] was followed.

Mice: All experiments were carried out in random bred male and female Swiss mice obtained from the Hoechst India Limited breeding house at Mulund, Bombay. The animals were free from Eperythrozoon coccoides. The animals received food pellets and water ad lib and were kept at 22-25° C room temperature.

Parasite : Plasmodium berghei K-173 strain drug-sensitive and berghei (NS) moderately resistant to chloroquine were obtained from the London School of Hygiene and Tropical Medicines. The strains produce lethal infection at 1×10^7 parasitized red blood cells per mouse when inoculated either intraperitoneally or intravenously, between 6 to 7 days post infection.

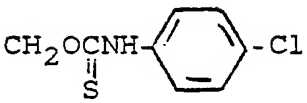
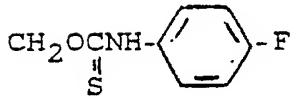
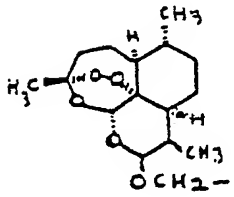
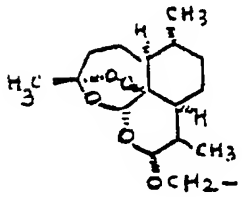
Administration of compounds: The compounds were administered orally or subcutaneously as per methods described by Raether and Fink [W.H.O. Report of the Scientific Working Group on the Chemotherapy in Malaria, TDR/Chemal 3rd Review, 85.3, Geneva, 3-5 June 1985 and references contained therein].

Compounds of the invention were homogenized in double refined Kardi oil or peanut oil or corn coil with one or two drops of polyoxyethylenesorbitan monooleate ((R)Tween-80, Sigma Chaniallo, England) and such suspensions were used for subcutaneous inoculation in mice. Drugs were administered for 5 days. 1st dosing was done within 2 hours of infection (D + 0) followed by D + 1, D + 2, D + 3 and D + 4.

Observation of the treated mice: The blood smears were prepared at different intervals from D + 4 and continued up to D + 28. Blood smears were drawn from the terminal end of the tail and stained in Giemsa. Mice which were free from berghei on D + 28 were considered as completely cured.

Results obtained with the compounds of Formula I of the invention are listed in Table 2.

Table 2 (cont.)

R	Dose mg/kg x 5	Route	Activity: No. of animals cured/ treated D + 7	Activity: No. of animals cured/ treated D + 28
	5	s.c.	12/12	12/12
	2.5	s.c.	6/6	3/6
	25	p.o.	6/6	6/6
	5	s.c.	5/5	6/6*)
	2.5	s.c.	5/5	2/5*)
	25	p.o.	5/5	5/5*)
	5	s.c.	6/6	6/6
	2.5	s.c	12/12	12/12
	1.25	s.c.	11/11	9/11
	25	p.o.	6/6	5/6
	5.0	s.c.	8/8	8/8 *)
	2.5	s.c.	8/8	7/8 *)
	5	s.c.	5/5	5/5
	2.5	s.c.	5/5	5/5
	25	p.o.	6/6	
	5	s.c.	6/6 *)	
	2.5	s.c.	6/6 *)	

Activity reported for all compounds is against chloroquine sensitive strain (P. berahei X-173). Activity reported with * is against chloroquine resistant strain.

nitrate (1.8 g) in water (3.0 ml) was added. To this stirred reaction mixture a solution of sodium hydroxide (0.4 g) in water (2.0 ml) was added dropwise. The reaction mixture was stirred for further 2 hours at room temperature. The residue was then filtered and washed with 5.0 ml of aqueous alcohol. Alcohol was removed from the combined filtrate, under vacuum. The aqueous layer was diluted with water and extracted with chloroform (2 X 10 ml). The aqueous layer was then acidified with acetic acid. Extraction of the acidified layer followed by concentration of extract and crystallisation from isopropyl ether - petroleum ether gave the title product; 0.72 g (75.79%) m.p. 166-167° C.

Example 5

3α,11α-Epoxy-3,4,5,5aα,6,7,8,8a,9,11,11a-undecahydro-9-(2-propynoxy)methyl-3β,6α,9-trimethylfurano[3,4-j]-[1,2]-benzodioxepin

To the stirred, ice cold, suspension of NaH (20 mg) in DMF (0.5 ml), propargyl bromide (0.1 ml) and 3α,11α-Epoxy-3,4,5, 5aα,6,7,8,8a,9,11,11a-undecahydro-9-hydroxymethyl-3β,6α,9-trimethylfurano[3,4-j][1,2]-benzodioxepin (60 mg) were added. The reaction mixture was slowly brought to room temperature and stirred for 2 hr. Water was then added to the reaction mixture and the product was extracted in petroleum ether (60-80° C). The product was purified by flash chromatography over silica gel; m.p. 105° C, yield 71%. Similarly following compounds were prepared, using appropriate halide in place of propargyl bromide.

3α,11α-Epoxy-3,4,5,5aα,6,7,8,8a,9,11,11a-undecahydro-9-(N,N-diethylaminoethoxy)methyl-3β,6α,9-trimethylfurano[3,4-j][1,2]-benzodioxepin, an oil, yield 47 %.

3α,11α-Epoxy-3,4,5,5aα,6,7,8,8a,9,11,11a-undecahydro-9-(2-propenoxy)methyl-3β,6α,9-trimethylfurano-[3,4-j][1,2]benzodioxepin, an oil, yield 45 %.

3α,11α-Epoxy-3,4,5,5aα,6,7,8,8a,9,11,11a-undecahydro-9-(3-phenyl-2-propenyloxy)methyl-3β,6α,9trimethylfurano[3,4-j]-[1,2]benzodioxepin, an oil, yield 42 %.

Example 6

3α,11α-Epoxy-3,4,5,5aα,6,7,8,8a,9,11,11a-undecahydro-9-(chloroacetoxy)methyl-3β,6α,9-trimethylfurano[3,4-j][1,2]-benzodioxepin

To the stirred solution of dimethylaminopyridine (DMAP) (0.1 g) in chloroform at room temperature chloroacetylchloride (0.1 ml) was added. The resulting mixture was stirred for 20 mins and then 3α,11α-epoxy-3,4,5, 5aα,6,7,8,8a,11,11a-undecahydro-9-hydroxymethyl-3β,6α,9-trimethylfurano[3,4-j][1,2]-benzodioxepin (0.07 g) was added. The reaction mixture was stirred for further 3 hrs. Water was added to the reaction mixture and the product was extracted in petroleum ether. The petroleum ether extract was washed with dil. HCl, water, dried (Na_2SO_4) and solvent removed. The product when purified by flash chromatography over silica gel was obtained, as an oil, yield 42%.

Similarly following compounds were prepared using appropriate acid chloride in place of chloroacetyl-chloride.

3α,11α-Epoxy-3,4,5,5aα,6,7,8,8a,11,11a-undecahydro-9-(4-chlorobutyryloxy)methyl-3β,6α,9-trimethylfurano[3,4-j][1,2]-benzodioxepin, an oil, yield 35 %.

Example 7

Preparation of 3α,11α-Epoxy-3,4,5,5aα,6,7,8,8a,9,11,11a-undecahydro-9-methylsulfonyloxymethyl-3β,6α,9-trimethylfurano[3,4-j][1,2]benzodioxepin

A mixture of 3α,11α-epoxy-3,4,5,5aα,6,7,8,8a,11,11a-undecahydro-9-hydroxymethyl-3β,6α,9-trimethylfurano[3,4-j]-[1,2]benzodioxepin (0.06 g) and methanesulfonylchloride (0.1 ml) in pyridine (0.3 ml) was heated at 90-100° C for 3 hrs. The reaction mixture was then cooled, diluted with water and the product was extracted with ethyl acetate. The ethyl acetate extract was washed with diluted acetic acid, water, aqueous sodium bicarbonate, water, dried (Na_2SO_4) and solvent removed to get an oil. The product was purified by flash chromatography over silica gel.

Similarly following sulfonate esters were prepared using appropriate sulfonyl chlorides in place of methylsulfonylchloride.

3α,11α-Epoxy-3,4,5,5aα,6,7,8,8a,11,11a-undecahydro-9-(p-toluenesulfonyloxy)methyl-3β,6α,9-trimethylfurano[3,4-j]-[1,2]benzodioxepin, an oil, yield 33 %.

benzodioxepin-9-carboxylate, an oil, yield 38 %.

2-Bromoethyl 3α,11α-epoxy-3,4,5,5aα,6,7,8,8a,9,11,11a-undecahydro-3β,6α,9-trimethylfurano[3,4-j][1,2]-benzodioxepin-9-carboxylate, an oil, yield 47 %.

3-Chloropropyl 3α,11α-epoxy-3,4,5,5aα,6,7,8,8a,9,11,11a-undecahydro-3β,6α,9-trimethylfurano[3,4-j]-[1,2]benzodioxepin-9-carboxylate, an oil, yield 24 %.

Ethyl 3α,11α-epoxy-3,4,5,5aα,6,7,8,8a,9,11,11a-undecahydro-3β,6α,9-trimethylfurano[3,4-j][1,2]-benzodioxepin-9-carboxylate, an oil, yield 29 %.

8-Chlorooctyl 3α,11α-epoxy-3,4,5,5aα,6,7,8,8a,9,11,11a-undecahydro-3β,6α,9-trimethylfurano[3,4-j][1,2]-benzodioxepin-9-carboxylate, an oil, yield 21 %.

Example 11

Preparation of 1-(3α,11α-Epoxy-3,4,5,5aα,6,7,8,8a,9,11,11a-undecahydro-3β,6α,9-trimethylfurano[3,4-j][1,2]-benzodioxepin-9-yl)-2,2'-dicarboethoxyethylene

A mixture of 3α,11α-Epoxy-3,4,5,5aα,6,7,8,8a,9,11,11a-undecahydro-3β,6α,9-trimethylfurano[3,4-j][1,2]-benzodioxepin-9-carboxaldehyde (0.08 g) diethyl malonate (0.3 ml), pyridine (0.3 ml) and piperidine (1.0 ml) was heated with stirring at 80° C for 16 hrs. The reaction mixture was cooled, treated with diluted HCl and was then extracted with petroleum ether (60-80). The extract was washed with water, dried (Na_2SO_4) and solvent removed. The residue was flash chromatographed over silica gel to get the title compound, as an oil, yield 22%.

Example 12

Preparation of 3α,11α-Epoxy-3,4,5,5aα,6,7,8,8a,9,11,11a-undecahydro-9-(cis-4-trifluoromethylstyryl)-3β,6α,9-trimethylfurano[3,4-j][1,2]benzodioxepin

To the stirred solution of the triphenyl p-trifluoromethylbenzyl phosphonium bromide (0.18 g) in dry tetrahydrofuran (2 ml), sodium hydride (0.03 g) was added. The reaction mixture was stirred for 30 mins at room temperature: 3α,11α-Epoxy-3,4,5,5aα,6,7,8,8a,9,11,11a-undecahydro-3β,6α,9-trimethylfurano[3,4-j]-[1,2]benzodioxepin-9-carboxaldehyde (5) (0.09 g) was then added to the above phosphonium ylide and the reaction mixture stirred for further 2 hrs. Water was then added to the reaction mixture and product extracted with chloroform. Residue from concentration of chloroform extract was purified by flash chromatography over silica gel, using chloroform as an eluant, first gave trans product in 9% yield. Further elution gave cis product in 26% yield.

Similarly following the conditions described using triethyl phosphonoacetate in place of triphenyl p-trifluoromethylbenzyl phosphonium bromide, the compound cis-1-(3α,11α-epoxy-3,4,5,5aα,6,7,8,8a,9,11,11a-undecahydro-3β,6α,9-trimethylfurano[3,4-j][1,2]benzodioxepin-9-yl)-2-carboethoxyethylene was obtained as an oil, yield 54 %.

Example 13

Preparation of 3α,12α-Epoxy-3,4,5,5aα,6,7,8,8aα,9,10,12β,12α-dodecahydro-10α-[3α,11α-epoxy-3,4,5,5aα,6,7,8,8a,9,11,11a-undecahydro-3β,6α,9-trimethylfurano[3,4-j][1,2]benzodioxepin-9-methylene]oxy-3β,6α,9β-trimethylpyrano[4,3-j]-[1,2]benzodioxepin

To a solution of dihydroartemisinin (0.490 g; 1.70 mmol) and 3α,11α-Epoxy-3,4,5,5aα,6,7,8,8a,9,11,11a-undecahydro-9-hydroxymethyl-3β,6α,9-trimethylfurano[3,4-j][1,2]benzodioxepin (0.350 gm; 1.23 mmol) in dry methylenechloride (70.0 ml) borontrifluoride etherate (0.2 ml) was added dropwise at 0° C. Reaction mixture was stirred for 15 minutes and then washed with water. The organic layer was separated, dried, filtered and filterate was concentrated. Residue obtained after concentration, was purified by flash chromatography using silica gel column to obtain the product. mp. 100° C, yield 21%.

Example 14

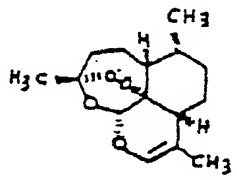
Preparation of 3α,12α-Epoxy-3,4,5,5aα,6,7,8,8aα,9,10,12β,12a-dodecahydro-10β[3α,11α-epoxy-3,4,5,5aα,6,7,8,8a,9,11,11a-undecahydro-3β,6α,9-trimethylfurano[3,4-j][1,2]benzodioxepin-9-methylen]oxy-3β,6α,9β-trimethylpyrano[4,3-j][1,2]benzodioxepin

$$\overset{\overset{X}{\|}}{CNR_5R_5'},$$

wherein X denotes O or S.

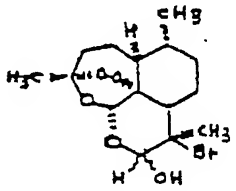
3. Compounds as claimed in claims 1 or 2 which are
3α,11α-Epoxy-3,4,5,5aα,6,7,8,8a,9,11,11a-undecahydro-9-formyl-3β,6α,9-trimethylfurano[3,4-j][1,2]-benzodioxepin,
3α,11α-Epoxy-3,4,5,5aα,6,7,8,8a,9,11,11a-undecahydro-9-(2-propynoxy)methyl-3β,6α,9-trimethylfurano-[3,4-j][1,2]-benzodioxepin,
3α,11α-Epoxy-3,4,5,5aα,6,7,8,8a,9,11,11a-undecahydro-9-(2-propenoxy)methyl-3β,6α,9-trimethylfurano-[3,4-j][1,2]-benzodioxepin,
3α,11α-Epoxy-3,4,5,5aα,6,7,8,8a,9,11,11a-undecahydro-9-(p-toluenesulfonyloxy)methyl-3β,6α,9-trimethylfurano-[3,4-j][1,2]benzodioxepin,
3α,11α-Epoxy-3,4,5,5aα,6,7,8,8a,9,11,11a-undecahydro-9-(4-chlorophenylaminothiocarbonyloxy)methyl-3β,6α,9-trimethylfurano[3,4-j][1,2]benzodioxepin,
3α,11α-Epoxy-3,4,5,5aα,6,7,8,8a,9,11,11a-undecahydro-9-(4-fluorophenylaminothiocarbonyloxy)methyl-3β,6α,9-trimethylfurano[3,4-j][1,2]benzodioxepin,
3α,12α-Epoxy-3,4,5,5aα,6,7,8,8aα,9,10,12β,12a-dodecahydro-10α-[3α,11α-epoxy-3,4,5,5aα,6,7,8,8a,9,11,11a-undecahydro-3β,6α,9-trimethylfurano[3,4-j][1,2]benzodioxepin-9-methylen]-oxy-3β,6α,9β-trimethylpyrano-[4,3-j][1,2]benzodioxepin und
3α,12α-Epoxy-3,4,5,5aα,6,7,8,8aα,9,10,12β,12a-dodecahydro-10β-[3α,11α-epoxy-3,4,5,5aα,6,7,8,8a,9,10,11,11a-undecahydro-3β,6α,9-trimethylfurnao[3,4-j][1,2]benzodioxepin-9-methylen]oxy-3β,6α,9β-trimethylpyrano-[4,3-j][1,2]benzodioxepin.

4. A process for the production of compounds of the formula I according to one or more of the preceding claims, wherein a compound of formula II



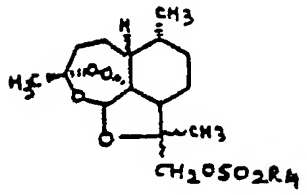
II

is treated with a brominating agent and subsequently hydrolyzed to a compound of formula III



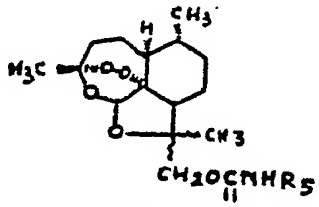
III

which is for the preparation of compounds of formula Ia



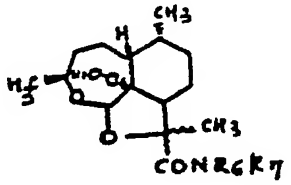
If

compounds of formula Ib are reacted with compounds of the formula R_4SO_2Cl
or wherein for the preparation of compounds of formula Ig



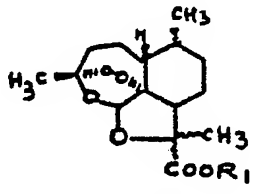
Ig

compounds of formula Ib are reacted with compounds of the formula R_5NCX,
or wherein for the preparation of compounds of formula Ih



Ih

compounds of formula Ic are reacted with thionylchloride and subsequently with compounds of the formula NR_6R_7,
or wherein for the preparation of compounds of the formula Ii



Ii

compounds of formula Ic are reacted with thionylchloride and subsequently with a compound of the formula R_1OH
or wherein for the preparation of compounds of the formula Ij

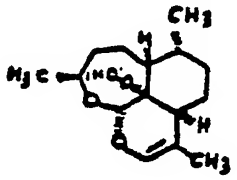
wherein R_3 stands for alkyl, substituted alkyl group, or a group SO_2R_4, wherein R_4 stands for alkyl or aryl group, or a group

$$CNR_5R_5',$$
$$\overset{*}{X}$$

wherein X denotes O or S,
R_5 stands for hydrogen,
R_5' stands for alkyl or aryl group or
NR_5R_5', stands for heterocycle;
$CONR_6R_7$,
wherein R_6 stands for hydrogen, aralkyl, R_7 stands for hydrogen, alkyl, aryl, aralkyl group or R_6 and R_7 together with the nitrogen to which they are attached form a heterocycle which may contain an additional hetero atom and is optionally substituted at one or more places;

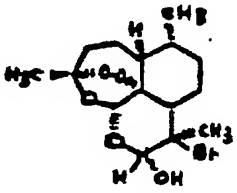
$CH = CR_8R_9$,

wherein R_8 stands for hydrogen, carboxyalkyl and R_9 stands for carboxyalkyl, aryl or heterocycle;
$COSR_{10}$,
wherein R_{10} stands for alkyl, substituted alkyl or aryl groups;
and pharmaceutically acceptable salts thereof, wherein a compound of formula II



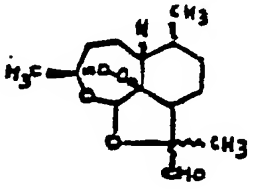
II

is treated with a brominating agent and subsequently hydrolyzed to a compound of formula III



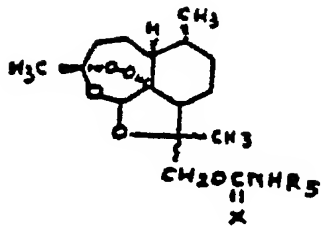
III

which is for the preparation of compounds of formula Ia



Ia

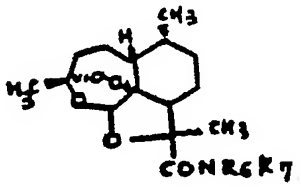
treated with an organic base, or wherein, for the preparation of compounds of formula Ib,



Ig

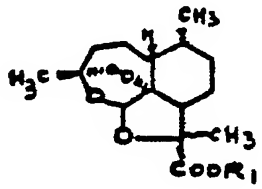
compounds of formula Ib are reacted with compounds of the formula R_5NCX,

or wherein for the preparation of compounds of formula Ih



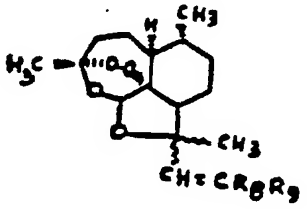
Ih

compounds of formula Ic are reacted with thionylchloride and subsequently with compounds of the formula NR_6R_7,
or wherein for the preparation of compounds of the formula Ii



Ii

compounds of formula Ic are reacted with thionylchloride and subsequently with a compound of the formula R_1OH
or wherein for the preparation of compounds of the formula Ij



Ij

wherein R_8 and R_9 stand for carbethoxy a compound of the formula Ia is treated with compounds of the formula $CH_2R_8R_9$
or wherein for the preparation of compounds of the formula Ij, wherein R_8 stands for hydrogen and R_9 stands for carboalkyl, aryl or a heterocycle,
a compound of the formula Ia is treated with compounds of the formula $Ph_3P=CHR_9$,
the substituents R_1 - R_9 having - where not especially defined - the same meanings as defined in connection with formula I.

2. A process for the production of compounds of formula I as claimed in claim 1, wherein R stands for CHO or CH_2OR_2,R_2 denoting hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, dialkylamino alkyl group or 3α,12α-Epoxy-3,4,5,5aα,6,7,8,8aα,9,10,12β,12a-dodecahydro-3β,6α,9β-trimethylpyrano[4,3-j][1,2]benzodioxepin-10-yl or a group COR_3, wherein R_3

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application number: EP 91 10 7304

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
X	WO-A-88 04 660 (SRI INTERNATIONAL) * Claims 6,28 * --	1,7	C 07 D 493/20 A 61 K 31/34// (C 07 D 493/20 C 07 D 323:00 C 07 D 321:00 C 07 D 307:00)
A	EP-A-0 362 730 (HOECHST AG) * Claims 1,6-8 * ----	1,7,8	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

C 07 D 493/00
A 61 K 31/00

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.

Claims searched completely: 1-8
Claims searched incompletely:
Claims not searched: 9,10
Reason for the limitation of the search:

Method for treatment of the human or animal body by surgery or therapy (See art. 52(4) of the European Patent Convention)

Place of search	Date of completion of the search	Examiner
THE HAGUE	08-07-1991	VOYIAZOGLOU

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
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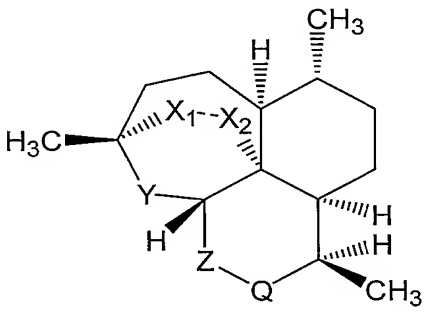
T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO Form 1505.1. 03.82

Pending Claims (April, 2010)

1. A pharmaceutical composition for treating infections caused by *Flaviviridae* sp., comprising an effective amout of a sesuiterpene having the formula:



wherein:

X_1 and X_2 are selected from the group consisting of O, S, Se and N;

Y is selected from the group consisting of O, S, Se, and N;

Z is selected from the group consisting of O, NH, S, and Se, and

Q is selected from the group consisting of CO, CHOH, $CHOCH_3$, $CHOC_2H_5$, $CHOC_3H_7$, and $CHOCOCCH_2CH_2COOH$,

and the pharmaceutically acceptable salts thereof.

2. A composition as defined in claim 1, wherein the sesquiterpene is selected from the group consisting of artemisinin and analogs of artemisinin.

3. A composition as defined in either claim 1 or claim 2, wherein the infection is hepatitis C.

4. A composition as defined in either claim 1 or claim 2, wherein the infection is bovine viral diarrhea or classical swine fever.

5. A pharmaceutical composition for treating infections caused by *Flaviviridae* sp. comprising an effective amount of an endoperoxide in combination with interferon or peg-interferon.

6. A composition as defined in claim 5, wherein the endoperoxide is selected from the group consisting of artemisinin and analogs of artemisinin.

7. A composition as defined in claim 5, wherein the infection is hepatitis C.

8. A pharmaceutical composition for treating infections caused by (+) sense RNA viruses, comprising an effective amount of an endoperoxide.

9. A composition as defined in claim 8, wherein the endoperoxide is selected from the group consisting of artemisinin and analogs of artemisinin.

10. A composition as defined in claim 8, where in the peroxo linkage (-O-O-) of the endoperoxide is substituted with a moiety selected from the group comprising -S-S-, -Se-Se-, -N-O-, and -N-N- linkages, and all combinations thereof.

11. A pharmaceutical composition for treating infections caused by (+) sense RNA viruses, comprising an effective amount of an endoperoxide in combination with interferon or peg-interferon.